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Structural Characterization of the Catalytic Active Site in the Latent and Active Natural Gelatinase B from Human Neutrophils

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ABSTRACT: Matrix metalloproteinases (MMPs) are endopeptidases that have a leading role in the catabolism of the macromolecular components of the extracellular matrix in a variety of normal and pathological processes. Human gelatinase B is a zinc-dependent proteinase and a member of the MMP family that is involved in inflammation, tissue remodeling, and cancer. We have conducted X-ray absorption spectroscopy (XAS), atomic emission, and quantum mechanics studies of natural and activated human gelatinase B. Our results show that the natural enzyme contains one catalytic zinc ion that is central to catalysis. In addition, upon enzyme activation, the catalytic zinc site exhibits a conformation change that results in the expansion of the bond distances around the zinc ion and the replacement of one sulfur with oxygen. Interestingly, quantum mechanics calculations show that oxygen ligation at the catalytic zinc ion exhibits a greater affinity to the binding of an oxygen from amino-acid residue rather than from an external water molecule. These results suggest that the catalytic zinc ion plays a key role in both substrate binding and catalysis.